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Chronic spontaneous urticaria following COVID-19 vaccination

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Introduction

We report a case series of eight patients who developed chronic spontaneous urticaria (CSU) following vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Table I).

Report of Cases

The median age of patients was 56.5 years (range, 27 to 78 years) and 75% (n= 6) were women. Wheals and/or angioedema occurred a median of 8.6 days (range, 1 to 18 days) after vaccination. All patients presented with wheals and five also presented with angioedema (Fig.1.). None of the patients presented with anaphylactic symptoms and inducible urticaria was excluded. Acute urticaria following vaccination was initially suspected. However, as wheals and/or angioedema lasted for more than 6 weeks in all patients, a diagnosis of CSU was made according to international EAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines.¹

Wheals and/or angioedema appeared for the first time following the administration of the first vaccine dose for six patients and after second dose of vaccine for two patients. Three patients received the BNT162b2 vaccine (Pfizer/BioNTech), one received the mRNA-1273 vaccine (Moderna), and four received the ChAdOx1 nCoV-19 Vaccine (AstraZeneca). Three patients reported an exacerbation of urticaria after the second dose and one patient after the third dose. Two patients discontinued their vaccination protocol due to concern for further urticaria exacerbation.

The mean duration of follow-up was 9.9 months (range from 8 to 11 months). All patients received H₁-antihistamines, two received short-course systemic corticosteroids, one received cyclosporine and two received omalizumab. Four patients were asymptomatic at the end of the follow-up period (5 to 11 months) and were able to discontinue the treatment. The mean

duration of CSU for these four patients was 6.8 months (range from 5 to 9 months). In contrast, four other patients were still symptomatic at follow-up, with a CSU duration of 8 months (n=1), 9 months (n=1) and 11 months (n=2).

One patient who developed severe arthritis 2 months after vaccination was subsequently diagnosed with systemic lupus erythematosus (SLE). None of the patients had a history of CSU before COVID-19 vaccination, but one patient reported a history of transient cholinergic urticaria 30 years earlier.

Discussion

Disease onset following vaccine may be coincidental or related to the vaccination. Since the incidence of CSU in the general population at the same time is not known however, it is not possible to define whether the prevalence was higher during this vaccination period. However, the short delay between vaccinations and the first symptoms of urticaria in our patients (median of 8.6 days) with no prior history of CSU and the exacerbation in four patients after the second or third vaccine dose, raise the possibility that the vaccines served as a trigger. Clinical experience suggests that vaccinations, as well as infections, are exacerbating factors of CSU. However, data in this area are sparse.

Acute urticaria and anaphylaxis have been described after COVID-19 vaccines.^{2,3} Exacerbations of CSU after COVID-19 vaccines have also been described.⁴ A few cases of new-onset CSU following COVID-19 vaccination have been published and are summarized in Table II.⁵⁻⁷ For instance, Magen *et al.* reported 27 patients with relapse of CSU and 32 patients with new-onset CSU within 3 months after the BNT162b2 vaccine.⁸ The latter authors have previously described a case series of new-onset CSU occurring 4 to 16 days after vaccination

with adjuvanted vaccines.⁹ In our series, CSU followed adenoviral vector or mRNA vaccines, neither of which are adjuvanted vaccines.

Although a coincidence cannot be ruled out, these observations of CSU following COVID-19 vaccination raise questions about their etiopathogenic mechanism. During SARS-CoV-2 infections and vaccination, mast cells could be activated through different mechanisms. They can be triggered by pathogen-associated molecular patterns via the activation of toll-like receptors. Furthermore, viral infections may stimulate mast cell degranulation via complement activation. Mast cells also express angiotensin converting enzyme 2 (ACE2), now known as a receptor for SARS-CoV-2.¹⁰

Moreover, in the specific case of CSU, an autoimmune pathway is implicated. For instance, several patients with CSU also have a concomitant autoimmune disease or family history of autoimmune disease, and/or the presence of some autoantibodies. Therefore, molecular mimicry in patients with genetic predispositions to autoimmune diseases could be one hypothesized mechanism for the development of CSU. The immune response induced by SARS-CoV-2 infection or vaccination, although primarily against viral antigens, could target host molecules that share sequence homology or structural similarities with viral epitopes. Indeed, studies have shown similarity and homology between SARS-CoV-2 proteins and human tissue antigens.¹¹ Moreover, antibodies to SARS-CoV-2 could bind some human tissue antigens.^{11,12} This cross-reactivity in patients with pre-existing self-tolerance deregulations may lead to development of autoimmune disease. Concomitant occurrence of SLE in one of our patients possibly supports this hypothesis. However, a delay for urticaria onset of 1 to 4 days after vaccination (observed in three of our patients), seems too short to involve an autoimmune reaction, unless these patients had previously been infected by SARS-CoV-2 infection. These patients had no history of symptomatic SARS-CoV-2 infection; however, anti-nucleocapsid

antibody was not performed. If this cross-reactivity could occur after vaccination, it should also occur after SARS-CoV-2 infection. However, our literature search revealed no reported onsets of CSU after SARS-CoV-2 infection. This may possibly be due to the delay or avoidance of medical care during the pandemic and/or to newly diagnosed CSU not being associated with the virus or being attributed to other triggering factors, such as lockdown and pandemic stress or medications (anti-inflammatory drugs) or because many patients have asymptomatic SARS-CoV-2 infection so the link could not be made.

Despite the absence of anaphylaxis or contraindications to the continuation of the vaccination protocol, because CSU is potentially disabling, its occurrence could lead to vaccination interruption, as was observed in two of our patients. It is important to inform patients not to interrupt vaccination after the onset of urticaria (acute or chronic) and to encourage them to complete the full protocol as recommended by international health organizations. Dermatologists can lend their expertise to help control/treat/minimize cutaneous reactions that may be triggered by the vaccines, including CSU. For instance, the administration or increase of H₁-antihistamines around the time of vaccination could reduce or avoid urticaria flare and allow patients to continue vaccination protocols.

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Figure legend:

Fig.1. Patient 2 - Urticarial lesions on the patient's lower limbs (A), upper limbs and trunk (B) 8 weeks after first dose of Moderna vaccine, treated by H₁-antihistamines up dosing (4 tablets a day) and a short course of methyprednisolone.

Patient No.	Sex	Age (y)	Vaccine			Urticaria onset after	Delay of onset (days)	Flare-up after second dose	Flare-up after third dose	Wheals/Angioedema	History of CU	Treatment of CSU	Concomitant AI disease	Duration of CSU (months)	Duration of follow-up since CSU onset (months)	CSU resolution
			1 st dose	2 ^d dose	3 ^d dose											
1	F	76	AZ	AZ	Moderna	1 st dose	1	yes	no	wheals and angioedema	no	antiH1, omalizumab	no	At least 11	11	no
2	M	48	Moderna	Moderna	Pfizer	1 st dose	2	yes	no (resolution of CSU before 3 ^d dose)	wheals	no	antiH1 sCS, cyclosporine	no	5	10	resolution for 5 months
3	F	38	Pfizer	Pfizer	Pfizer	1 st dose	7	onset	no (resolution of CSU before 3 ^d dose)	wheals and angioedema	no	antiH1 sCS	SLE	9	10	resolution for 1 month
4	F	78	Pfizer	Pfizer	vaccination discontinued	1 st dose	18	yes, after second dose	vaccination discontinued	wheals and angioedema	cholinergic urticaria	antiH1	no	6	10	resolution for 4 months
5	F	43	AZ	vaccination discontinued	vaccination discontinued	1 st dose	4	vaccination discontinued	vaccination discontinued	wheals	no	antiH1	no	at least 11	11	no
6	M	70	AZ	AZ	Pfizer	2 ^d dose	15	onset	no	wheals and angioedema	no	antiH1	no	7	10	resolution for 3 months
7	F	72	Pfizer	Pfizer	Pfizer	1 st dose	7	no	no	wheals	no	antiH1, omalizumab	no	at least 9	9	no
8	F	27	AZ	AZ	Moderna	2 ^d dose	15	onset	yes	wheals and angioedema	no	antiH1	no	at least 8	8	no

Table I: Patients' clinical data. ChAdOx1 nCoV-19 Vaccine AstraZeneca (AZ), H₁-antihistamines (antiH1), autoimmune disease (AI disease), chronic urticaria (CU), mRNA-1273 vaccine Moderna (Moderna), BNT162b2 vaccine Pfizer/BioNTech (Pfizer), systemic corticosteroids (sCS), systemic lupus erythematosus (SLE), topical corticosteroids (tCS), years (y). CSU resolution means no more wheals and/or angioedema and patients were able to discontinue their treatment.

Number of cases	Sex	Age (y)	Vaccine	Urticaria onset after	Delay of onset	Flare-up after second/third dose	Treatment of CSU	Duration of CSU	Resolution	Publication reference	Publication type
1	M	20	Pfizer	2 ^d dose	7 days	not specified	antiH1	at least 8 weeks	no	5	case report
1	M	60	AZ	1 st dose	5 days	yes, mild flare with 2 ^d dose (Pfizer)	antiH1 sCS, tCS	3 months	yes	7	case report
1	M	39	AZ	2 ^d dose	14 days	vaccination discontinued	antiH1 sCS	at least 6 months	no	6	case report
32	21 F / 11 M	41.2+/- 11.5*	Pfizer	1 st or 2 ^d dose	+/- 3 months**	no specified	not specified	not specified	not specified	8	retrospective study

Table II: Summary table of published data of new onset CSU after SARS-CoV-2 vaccination. ChAdOx1 nCoV-19 Vaccine AstraZeneca (AZ), H₁-antihistamines (antiH1), mRNA-1273 vaccine Moderna (Moderna), BNT162b2 vaccine Pfizer/BioNTech (Pfizer), systemic corticosteroids (sCS), topical corticosteroids (tCS), years (y). CSU resolution means no more wheals and/or angioedema and patients were able to discontinue their treatment.

* mean+/- standard deviation

** Patients included if urticaria began within 3 months of vaccination.

